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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/485,943	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,132-137,139-143,145-153,155-159 and 163-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124, 132-137, 139-143, 145-153, 155-159 and 163-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 10-3-05 mistakenly says claims 1-124 have been canceled. Only claims 1-123 have been canceled.

Claims 1-123, 125-131, 138, 144, 154 and 160-162 have been canceled. Claims 124, 132-137, 139-143, 145-153, 155-159 and 163-173 are pending and under consideration in the instant office action.

Applicant's arguments filed 10-3-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The sequences on pg 158, line 5 (two) and in claims 167 and 168 (gly-ser-pro) have been amended to include SEQ ID NOs.

The status of the applications on pg 1, lines 8-11 (three) and pg 12, line 2 (two), have been updated.

Claim Rejections - 35 USC § 112

Enablement

Claims 124, 132-137, 139-143, 145-149, 155-159 and 163-173 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Breadth of the claims

The claims are drawn towards a method of modifying the weight of a mammal using a vector encoding an ob protein under conditions that provide for expression of the ob protein in vivo. The ob proteins in the claims include SEQ ID NO: 2 (mouse ob), SEQ ID NO: 4 (human ob) and variations thereof (see claims for details regarding the variations). The preamble of the claim 124 requires "modifying the body weight of a mammal". The body of the claim requires administering the vector to a mammal "under conditions that provide for expression of ob polypeptide in vivo, such ob polypeptide capable of modulating body weight". The body of the claim requires the body weight of the mammal is modified. Therefore, administration of a vector encoding ob must decrease body weight to have an enabled use according to the specification.

State of the art regarding the ob gene/protein

The obese (ob) gene product is equivalent to the leptin gene product (Tartaglia, 1995, Cell, Vol. 83, pages 1263-1271; see abstract, line 1; see the instant application on pg 5, lines 5-16).

Ob/ob mice with a homozygous disruption in the ob gene were known to be obese (pg 3, lines 3-6).

At the time of filing, it was unknown whether obese ob/ob mice correlated to obese humans with a gene mutation. Since the time of filing, Clayton (Arch. Dis. Child,

1998, Vol. 78, 278-284) taught that 5% of humans with obesity have an ob concentration lower than expected (pg 282, col. 1, line 20).

The specification states: "Because of the myriad factors that seem to impact body weight, it has not been possible to predict which factors and, more particularly, which homeostatic mechanisms is actually primarily determinative. Nonetheless, the apparent connections between the ob gene and the extent and characteristics of obesity have prompted the further investigation and elucidation that is reflected by the present application. It is the identification of the sequence of the gene and corresponding peptide materials, to which the present invention following below directs itself." (pg 4, lines 14-20).

Thus, it was unpredictable whether ob/ob mice correlated to any obese human or to a gene disruption that occurred in humans.

At the time of filing, the art did not teach what tissue expressed the ob protein. Nor did the art teach in what tissues the ob protein mediated an effect. Since the time of filing, Tartaglia (cited above, Dec. 29, 1995, Cell, Vol. 83, pages 1263-1271) confirmed that up to 1995, the tissue in which the ob protein mediated an effect remained unknown (pg 1263, col. 2, line 2).

Thus, the tissue target required to express ob or to mediate a decrease in body weight in a mammal was unknown at the time of filing.

Since the time of filing, Fletcher (Nov. 15, 1995, Blood, Vol. 86, page 241a) taught decreasing the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced

with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12).

Morsy (1998, Proc. Natl. Acad. Sci., USA, Vol. 95, pages 7866-7871) taught that 60% weight loss can be obtained for 6-7 weeks following administration of a leptin-encoded adenoviral vector (pg 7870, col. 1, line 13); however, analysis revealed eventual loss of the vector DNA 4 and 8 weeks following administration of the vector (pg 7870, col. 2, line 5).

Unpredictability of gene therapy

At the time of filing and since, the combination of vector, promoter, dosage, target tissue, level of expression and route of administration required to target the desired tissue so that a therapeutic would occur was unpredictable.

Feldman (Fundamental & Clinical Pharmacology, 1995, Vol. 9, pg 8-16) suggested treating restenosis using a vector encoding a protein. Feldman discussed experiments in which the vector administered to the arterial wall during angioplasty allowed low levels of protein expression in cells of the arterial wall. Feldman taught that obtaining a therapeutic effect was prevented by low numbers of cells expressing a transgene, transfection efficiency, target specificity, and sustained expression (pg 12, "Arterial gene therapy"). None of the experiments described by Feldman resulted in a therapeutic effect.

Miller (Feb. 1995, FASEB J., Vol. 9, pg 190-199) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be

advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Miller did not obtain a therapeutic effect using gene delivery.

Crystal (Oct. 20, 1995, Science, Vol. 270, pg 404-410) also reviewed various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409). Crystal did not obtain a therapeutic effect using gene delivery.

Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviewed vectors for use in gene therapy and discussed problems associated with adenoviral vectors and indicates a resolution to vector targeting has not been achieved in the art (see entire article). Verma also taught appropriate regulatory elements may improve expression, but it is unpredictable what regulatory elements target what tissues (pg 240, sentence bridging col. 2-3). Verma did not obtain a therapeutic effect using gene delivery.

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed new techniques under experimentation in the art that show promise but stated that such techniques were even less efficient than viral gene delivery that failed to work (see pg 65, 1st ¶ under "Conclusion"). Deonarain did not obtain a therapeutic effect using gene delivery.

Ross (Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790) stated a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (pg 1782, col. 2, 1st full ¶). The ability to use gene therapy to obtain a therapeutic effect in a patient was unpredictable (Ross, pg 1789, col. 1, 1st ¶). Ross did not obtain a therapeutic effect using gene delivery.

Therefore, it was unpredictable what combination of vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic effect using gene delivery.

Teachings of the specification

Pg 5, line 10 teaches the "leptin" protein is absent in plasma of ob/ob mice. The specification does not teach the leptin protein is absent in obese humans.

The specification on pg 73-83 describes protein-based therapy for obesity. On pg 74, lines 18-27, applicants describe administering the ob protein by intravenous, intraarterial, intraperitoneal, intramuscular or subcutaneous routs of administration. Pg 83, line 3, through pg 84, line 24, describes administering the ob gene using a vector to decrease body weight of a mammal. The description of nucleic acid-based therapies on pg 83 does not include a description of the conditions required to obtain expression of the protein or the route of administration. The disclosure on pg 74 is limited to protein administration and does not include vector administration. One of skill in the art would not read the description of routes of administration for proteins on pg 74 as applying to the nucleic acid-based therapy on pg 83 because they are under different headings (see

headings for "Polypeptide-based therapeutic treatment" and "Nucleic acid-based therapeutic treatments" on pg 73 and 83, respectively). The specification does not teach any specific dosages or routes of delivery for the vectors listed for use in *in vivo* gene delivery.

Pg 83, line 4, teaches the ob gene can be "introduced into human fat cells to develop gene therapy for obesity." The specification does not teach how to target vectors to adipocytes using *in vivo* gene delivery. The specification does not teach what cells mediate the function of the ob protein so that one of skill could target a vector encoding ob to those cells.

Pg 83, lines 3-26, lists viral vectors for delivering the ob gene. For example, defective viral vectors allow "for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Thus, adipose tissue can be specifically targeted." Such vectors include HSV, papillomavirus, EBV adenovirus, AAV and retrovirus. Pg 84, lines 1-17, describes introducing a vector by lipofection. Pg 84, lines 18-24 describe administering the vector as naked DNA plasmid. The specification does not teach the specific combination of vector, promoter, route of administration and dosage required to obtain ob expression in a mammal such that a decrease in body weight is obtained.

Pg 90 begins the examples section, which include gene mapping of the mouse and human ob gene, cloning of the mouse and human ob gene, preparing the ob protein, preparing antibodies to the ob protein and recombinant expression of the ob protein in bacteria.

Pg 118, line 23, pg 12, line 10, through pg 125, line 2, and pg 125, Table 1, teach administering the ob protein to three strains of ob/ob mice. The ob/ob mice lost weight.

Pg 129, Example 9, and pg 126, Example 10, describe increased expression of ob in adipocytes as compared to other tissues. Since the time of filing, it has been confirmed that ob was expressed exclusively in adipose tissue (Clayton, cited above, pg 282, col. 1, line 3).

Pg 144, line 22, and pg 120, lines 1-25, describe the ob serum levels in mice and humans.

Pg 147, Example 11, teaches the human ob protein is active in ob/ob mice.

The specification teaches delivering ob protein to treat obesity on pg 73-74 but does not provide adequate guidance for one of skill to obtain the same serum level ob using gene delivery.

Overall, the specification does not overcome the unpredictability in the art by teaching the specific combination of vector, promoter, dosage and route of administration required to target ob expression to fat cells or how to express ob protein so it will target the tissue that mediates a reduction in body weight.

Since the time of filing, Fletcher (cited above) decreased the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12). In view of the unpredictability in the art of gene therapy, the specific combination of retrovirus, transduced bone marrow cells and bone marrow administration is essential to the

invention. Applicants do not enable the claimed invention because applicants do not describe the specific combination of retrovirus, transduced bone marrow cells and bone marrow administration, which is essential to reduce body weight as taught by Fletcher.

Morsy (cited above) obtained weight loss by administering 1-2 x 10^{11} particles of helper adenoviral vector encoding leptin via the tail vein of ob/ob mice (pg 7869, col. 2; pg 7870, Fig. 4B, Fig. 5B, col. 1). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles is essential to the invention. Given the state of the art regarding the ob gene/protein taken with the teachings in the specification, one of skill would not have expected intravenous administration to cause ob expression in adipocytes as contemplated by applicants as being the source of ob expression. Nor would one of skill have known that intravenous administration would cause ob expression capable of targeting cells that mediate a therapeutic effect. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles, which is essential to reduce body weight as taught by Morsy.

Muzzin of record (PNAS, Dec. 1996, Vol. 93, pg 14804-14808) obtained weight loss of ob/ob mice by administering 3 x 10^{9} particle forming units of helper adenoviral vector encoding leptin via the tail vein (pg 14805, ¶ bridging col. 1-2 and col. 2, 1st full ¶). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 3 x 10^{9} pfu is essential to the invention. One of skill would not have expected that intravenous administration would cause

expression in adipocytes as contemplated by applicants as the source of the majority of ob expression. Nor would one of skill have expected that intravenous administration would cause ob expression capable of targeting cells capable of mediating a decrease in body weight. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 3×10^9 pfu, which is essential to reduce body weight as taught by Muzzin.

In view of the art recognized unpredictability in gene therapy and the mere list of possible vectors provided by applicants on pg 83 and 84 without teaching the route of administration or dosage, those of skill in the art would be left to perform an undue amount of experimentation to determine the specific combination of vector, promoter, route of administration and dosage required to reduce body weight in a mammal.

In addition, the claims encompass administering a vector encoding ob and obtaining any body weight modulation. However, the specification is clearly limited to administering a vector encoding ob to decrease body weight (pg 83, line 5). Therefore, the claims should be limited to decreasing body weight.

Furthermore, the claims encompass decreasing the body weight of any mammal using a vector encoding an ob protein. However, the specification and the art since the time of filing are limited to treating mammals with an ob deficiency with the ob protein. The specification does not correlate the obese mammals having a defective ob gene to any other obese mammals or any other obesity related gene defect. The specification does not provide an enabled use for decreasing the body weight of a wild-type mammal

(having a normal weight). Therefore, it would require one of skill undue experimentation to determine how to use the vector encoding ob to treat obesity in any mammal as broadly claimed other than those with a defective ob gene.

Certain claims encompass using any analog of an ob protein that modulates body weight. The specification defines analogs as ob proteins that agonize or antagonize the function of the ob protein. In other words, the claims encompass administering a vector encoding a protein that antagonizes the function of the ob protein and causes a weight increase. The specification does not teach any ob proteins that antagonize the function of ob. The specification does not teach how to use the ob protein analogs to increase weight. Without such guidance it would require one of skill in the art undue experimentation to determine antagonistic analogs of the ob protein or how to use vectors encoding ob proteins capable of increasing body weight.

Applicants argue Fletcher, Muzzin et al. used leptin gene therapy to treat ob/ob mice after the time of filing. Therefore, applicants conclude that the broad statement in the specification as originally filed were enabling. Applicants' argument is not persuasive. The specific combination of vector and route of administration described by Fletcher, Muzzin et al. are not disclosed in the specification as originally filed. Applicants did not teach the specific combination of vector, route of administration, etc. required to overcome the unpredictability in the art and decrease body weight using leptin gene therapy. Such parameters are essential for enabling the method because the combination of elements required to obtain a therapeutic effect using gene therapy was unpredictable.

The specification does not enable using a vector encoding an ob protein having any substitution as broadly encompassed by 134, 135, 142, 143, 148, 149, 158, 159 and 165-173. Salvador (Exp. Opin. Pharmacotherapy, 2001, Vol. 2, No. 10, pg 1615-1622) taught leptin is 167 amino acids in length and has the body weight control functions confined to amino acids residues 106-140. The specification teaches the conservative and non-conservative substitutions between the mouse and human leptin proteins in Fig. 4. The specification does not define what they consider "conservative" and "non-conservative" substitutions. The specification does not teach the functional region of the leptin protein or that any substitution as broadly claimed will allow the leptin protein produced to control body weight. Without such guidance it would have required one of skill undue experimentation to determine which amino acids could be substituted without altering the active site of leptin or to determine which amino acids could be substituted without altering the structure of the active site or the function of leptin.

Applicants' arguments have been considered but are not persuasive because they relate to making the substitutions. The rejection is based on enabling one of skill to use any of the substitutions in the method such that body weight will be reduced.

The specification does not enable "modifying" the body weight of a mammal by administering a vector encoding leptin as broadly claimed. The only body modification described by applicants when administering a vector encoding leptin is decreased body weight. Therefore, the claims should be limited to decreasing body weight.

New Matter

Claims 124, 132-137, 139-143, 145-149, 155-159 and 163-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "conditions that provide for expression of the OB polypeptide in vivo" in claims 124, 132-135, 163-165 and 167 remains new matter. Support cannot be found on pg 83-84, which merely lists possible vectors for gene delivery. The specification does not describe any dosage or route of administration for the vectors, which is encompassed by "conditions that provide for expression of the OB polypeptide in vivo." While it is readily apparent that the specification contemplates gene delivery, it is not readily apparent that applicants contemplated the conditions that would cause ob expression *in vivo* using gene delivery. The breadth of expressing the ob protein anywhere *in vivo* as broadly encompassed by the phrase is certainly not readily apparent from pg 83, line 4, which is limited to introducing the ob gene into human fat cells. Applicants argue the "conditions" are readily apparent. Applicants' argument is unfounded. Applicants argue the specification describes daily administration studies, infusion studies and dose response studies. Therefore, applicants conclude the "conditions" required to obtain a therapeutic effect are not new matter. Applicants' argument is not persuasive. The specific combination of vector, dose and route of

administration required to reduce body weight using leptin gene therapy is not disclosed. Therefore, the "conditions that provide for expression of the OB polypeptide in vivo whereby the body weight of the mammal is modified" as claimed are new matter.

Similar phrases are found in claims 139-143, 155-159, 166 and 168-173, which are rejected for the reasons in the paragraph above.

The phrase "operatively associated with an expression control sequence" in claims 139-143, 145-149 and 155-157 is new matter. Pg 51, lines 8-16, describes coding sequences "under the control" of transcriptional and translational control sequences. The scope of such sequences is not the same as "operatively associated with an expression control sequence." The section that describes *in vivo* gene delivery does not contemplate using the expression control sequences describe on pg 52, line 7, through pg 53, line 15. In context, the expression control sequences described on pg 52, line 7, through pg 53, line 15, are limited to in vitro expression of ob because they are part of the description of unicellular hosts for producing the protein *in vitro* (see pg 52, line 2; "yeast" on line 19; pg 53, lines 9-15; pg 54, lines 7-9). The section from pg 50, line 18, through pg 54, line 9, is headed "Production of OB polypeptide expression and synthesis" and discusses numerous culture methods, including bacterial, eukaryotic cell culture and yeast for expressing the ob protein, but does not discuss expressing the protein *in vivo*.

The concept of "83 percent or more amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOs: 2, 4, 5, 6, 23 or 25" in claim 133, 147 is new matter. Applicants argue the phrase has support on pg 12, line 26, through pg 13,

line 2. Applicants' argument is not persuasive. The description of Fig. 5 merely states the amino acid sequence of SEQ ID NO: 5 was derived from the murine ob gene in Fig. 3 and the shows the location of a signal sequence cleavage site.

The concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53... ...166 is substituted with another amino acid" in claims 134, 142, 148, 158 is new matter. Fig. 4 describes specific conservative substitutions of the amino acids of the mouse and human ob polypeptide using asterisks at amino acids 53, 92, 98, 118, 121, 122, 126-128, 132, 139, 159 and 166 and specific non-conservative substitutions using a dash at amino acids 71, 85, 89, 110, 129, 157 and 163. The specification does not suggest substituting the amino acids listed with any amino acid as broadly claimed.

Applicants argue the concept is readily apparent from Fig. 4. Applicants' argument is not persuasive. Fig. 4 is limited to specific substitutions and does not contemplate the broader substitutions claimed.

The concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids... ...56... [and] ...95... is substituted with another amino acid" in claims 134, 142, 148, 158 is new matter. Amino acids 56 and 95 are not marked as being substituted in Fig. 4.

The concept of an OB protein comprising "amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158,

162 and 165 is substituted with another amino acid" in claim 135, 143, 149, 159 is new matter. The specification does not suggest substituting the amino acids listed with any amino acid as broadly claimed. The numbers for substitutions as claimed do not correspond with the description in Fig. 4. In fact, the human protein is described in Fig. 4 as having 167 amino acids while the human protein is described in Fig. 5 as having 166 amino acids.

The concept of administering viral vectors by infection or liposome mediated transfection in claim 151 is new matter. Pg 83, lines 4-26, contemplates viral vectors but does not teach administering viral vectors to a mammal by infection. Pg 84, lines 1-17, contemplates delivering the ob gene by lipofection but does not teach lipofection is used to administer viral vectors. It is not readily apparent that the section discussing lipofection encompasses viral vectors in the preceding paragraphs because lipofection is used for nucleic acids (pg 84, line 2) and not for viral particles. Nowhere does the section on nucleic acid-based therapeutic treatments (pg 83, line 4, through pg 84, line 24) contemplate administering the viral vectors by infection or by lipofection.

Applicants point to pg 84, lines 1-17, but the examiner has pointed to this section of the specification and described why the cited section fails to support the phrase.

The concept of using the early or late SV40, CMV, vaccinia, polyoma, adenovirus, 3-phsphoglycerate kinase or other glycolytic enzyme promoters for gene delivery in a mammal as in claim 160 remains new matter because it does not have support in the specification as originally filed. In particular, it is not readily apparent that the expression control sequences for expressing ob in bacteria in vitro contemplated in

the paragraph bridging pg 52-53 are for gene delivery in vivo because pg 52, line 7, through pg 53, line 15, in context is limited to in vitro expression of ob (see pg 53, line 15, "human and plant cells in tissue culture"). Nowhere does pg 52, line 7, through pg 53, line 15, contemplate using the regulatory elements in vector for gene delivery in vivo as claimed.

Applicants point to pg 52, line 25-pg 53, line 8, but the examiner has pointed to this section of the specification and described why the cited section fails to support the phrase.

Claims 165-173 remain new matter. Applicants argue the claims have support on pg 32, line 15 through pg 35, line 11. Applicants' argument is not persuasive. The specific substitutions in claim 165, 166, 170, 171 and 173 cannot be found on pg 32, line 15, through pg 35, line 11. For example, the cited part of the specification does not contemplate substituting the serine at position 53 with glycine, alanine, valine, cysteine, methionine, or threonine as in claim 165. Please point to specific support for each substitution claimed. The N-terminal amino acids in claims 167 and 168 cannot be found. The "truncated analogs" with the substitutions listed in claims 169, 172 cannot be found.

Indefiniteness

Claim 140 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "such OB encoding DNA" in claim 140 lacks antecedent basis. "DNA encoding an OB polypeptide" in the preamble does not provide literal antecedent basis for the phrase.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER